MRS of Perinatal Asphyxia

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Introduction

Magnetic resonance spectroscopy provides the noninvasive detection of a number of important cellular metabolites and has become a valuable research and clinical tool to monitor normal and abnormal metabolism in the newborn brain [1-20]. Both phosphorus and proton MRS have been applied in pediatric studies, with the majority of the studies being proton MRS due to its greater inherent sensitivity. Phosphorus MRS studies have demonstrated the ability to monitor key metabolites such as adenosine triphosphate (ATP), phosphocreatine and inorganic phosphate in the pediatric brain and to detect significant bioenergetic changes following hypoxic-ischemic brain injury [10, 19]. While of great biologic interest, phosphorus MRS is severely limited in its clinical applicability due to low inherent sensitivity and its limited availability on clinical MR scanners. Since the phosphorus nucleus precesses at a different frequency, specialized excitation and reception hardware is required that is not typically provided with clinical MR scanners and the low inherent sensitivity limits the minimum volume to approximately 20 cm^3 for adequate signal-to-noise MRS data from the human brain.

Proton MR spectroscopy, however, can be performed routinely on most clinical MR scanners and has been applied in a wide range of pediatric applications [20]. This method is based on the detection of MR signals from hydrogen atoms that resonate at specific frequencies due to the particular molecular environment of the small mobile compounds observable by proton MRS. MR spectra are simply graphs of amplitude versus frequency in which the area under a “peak” is proportional to concentration. The common metabolites detectable at millimolar concentrations in the normal pediatric brain by proton MRS are N-acetyl aspartate (NAA), creatine, choline (including contributions from phosphocholine, and other choline-containing compounds), myoinositol, and composite resonances of glutamine, γ-aminobutyrate (GABA), and glutamate. This composite resonance is abbreviated Glx. In cases of brain injury, elevated lactate can be observed and, in cases of cellular necrosis, lipid resonances from membrane degradation can be observed. NAA has been shown in numerous studies to be a marker of neuronal function and is typically decreased following brain injury. Choline and related compounds are involved in membrane phospholipid synthesis and are elevated with increased cellular proliferation, including both normal and neoplastic growth. Myoinositol levels reflect changes in osmolality and glial cell density and thus can be altered due to a variety of pathological conditions.

Single Voxel Proton MR Spectroscopy of Normal Human Brain Maturation

Neonatal MR spectra are strikingly different from those of adult brain. In the newborn brain, the NAA resonance is much smaller than the choline resonance, whereas the NAA peak is much larger than the height of the choline peak in the adult brain. The metabolite concentrations and their ratios in babies change nonlinearly with age, and the most rapid changes occur in premature and term newborns [7,8]. Single voxel MRS studies of the developing brain were acquired from specific regions (e.g. occipital cortex, parieto-occipital white matter, and thalamus) with voxel sizes of typically

8 cm^3 [7,8]. By acquiring water unsuppressed spectra and measuring the relaxation times for each resonance, the absolute quantitation of each metabolite relative to water could be calculated providing estimates of concentration [8]. These studies showed that choline (and choline-containing compounds) were significantly higher in concentration by a factor of two as compared to adult values. These studies also demonstrated significantly lower concentrations for NAA in newborns and that NAA levels increased rapidly following birth.

More recently, short echo time, quantitative MRS was applied in a study of 28 exams of 21 newborns with gestational ages ranging from 32 to 43 weeks [21]. In this study, MR spectra were acquired from three anatomic locations, centrum semiovale for developing white matter, thalamus including both hemispheres, and occipital gray matter. Also, the spectra were analyzed using linear combination model fitting [22] of the short echo time spectra, considerably extending the range of observable metabolites to include acetate, alanine, aspartate, cholines, creatines, γ-aminobutyrate, glucose, glutamine, glutamate, glutathione, glycine, lactate, myo-inositol, macromolecular contributions, N-acetylaspartate (NAA), N-acetylaspartylglutamate, phosphoethanolamine, scyllo-inositol, taurine and threonine. Significant concentration changes with age and location were observed for many metabolites. In this study, significant increases in NAA, glutamate, creatines, and taurine were observed with early brain maturation as well as significant decreases in glutathione, lactate, myo-inositol, scyllo-inositol, and phosphoethanolamine. The most dramatic changes with maturation were the increased NAA and decreased myo-inositol [21]. Also, the results of this study demonstrated that, although some compounds were significantly reduced such as NAA and some elevated such as choline between premature (32 week gestational age) and term newborns, the total brain metabolite content was not significantly different.

MR Spectroscopic Imaging of Early Human Brain Maturation

Single voxel MRS acquisition is available on most clinical MR scanners and has been used in the vast majority of pediatric MRS studies. However, single voxel MR studies are limited in spatial coverage and spatial resolution. Especially for the small neonatal brain, it is problematic to attain accurate placement of the localized MRS volume to a specific anatomic location without spectral contamination from adjacent tissues. Single voxel MRS studies of the neonatal brain are limited to one or two regions and therefore cannot assess the spatial distribution of metabolites. To overcome this limitation, recent studies have added phase encoding techniques to obtain localized spectra from arrays of multiple contiguous voxels [23]. This technique, commonly termed MR spectroscopic imaging (MRSI), provides an assessment of spatial distribution of the various metabolites in addition to their relative concentrations within a voxel.

MRSI of premature and term newborns demonstrated the feasibility of detecting the 3D distributions of choline, creatine, and NAA resonances in the neonatal brain and significant ($p<0.05$) spectral differences were detected among anatomic locations and between the premature and term groups [16]. In premature newborns, regions such as the thalamus that mature earliest demonstrated the highest levels of NAA, whereas later maturing frontal white matter showed the lowest. The basal ganglia spectra showed the largest increase in NAA between term and premature infants, consistent with rapid maturation over this time period. This study demonstrated that MRSI can detect “metabolic maturation” in cellular metabolite levels and thus may be an important tool in

the assessing both normal and abnormal cerebral development in the pediatric brain. The significant differences in metabolite distributions and peak area ratios between the term and preterm infants show that metabolites vary with both topology and with brain maturation [16]. This study also indicated the need for determining topologic and age-matched normative values before metabolic abnormalities in neonates can be accurately assessed by MRS.

Single Voxel Proton MR Spectroscopy in Neonates with Abnormal Outcome:

Proton spectroscopy has shown significant potential for the early detection of brain injury in encephalopathic neonates [1-6, 14-15]. In the normal term infant, lactate is typically not seen in the brain parenchyma, although it may be present in the cerebrospinal fluid of normal neonate [24,25]. Lactate is seen in the brain within hours after injury, probably due to mitochondrial impairment and subsequent anaerobic glycolysis in brain parenchyma. The concentration of N-acetylaspartate (NAA), which increases as neurons mature and decreases with neuronal injury, is reduced within a few days of any injury [6]; the degree of reduction of NAA seems to correlate well with neurodevelopmental outcome [15]. Some investigators report an increase in glutamine/glutamate, as well [26]. Elevated lactate peaks (Lac/NAA ratios above 0.5, Lac/Cr ratios above 1, elevated Lac/Cho) have been shown to be associated with impaired neurological outcome at age 12 months [3,15]. A significant association (Table 1) was found between metabolite ratios (increased lactate/choline and lactate/NAA ratios in basal ganglia and WM) and poor 12 month neuromotor outcome [15]. All spectra obtained demonstrated the normal peaks of choline, creatine and NAA but many demonstrated a significant lactate resonance presumably due to cellular effects of hypoxic/ischemic injury. To determine whether lactate observation correlated with neurologic outcome, the MRS ratios were compared with neurodevelopmental exam findings at 1 year [15].

Table 1: Correlation of MRS Ratios in Basal Ganglia (BG) and Watershed (WS) Voxels with 1 Year Neuromotor (NM) Scores

NM Score	0	1	2-3	5-6
N of patients	13	7	7	4
BG Lac/Cho	0.02 (0.06)	0.06 (0.03)	0.12 (0.06)	0.42 (0.24)
BG Lac/NAA	0.11 (0.08)	0.14 (0.09)	0.13 (0.09)	0.48 (0.16)
WS Lac/Cho	0.10 (0.07)	0.20 (0.11)	0.13 (0.10)	0.48 (0.22)
WS Lac/NAA	0.21 (0.11)	0.28 (0.16)	0.33 (0.27)	1.10 (0.5)

Staistical Significance: BG Lac/Cho: p=0.0001, WS Lac/Cho: p=0.005, BG Lac/NAA: p=0.0003, WS Lac/NAA: p=0.01, BG NAA/Cho: p=0.001, WS NAA/Cho: p=0.001

MR Spectroscopic Imaging in Neonates with Abnormal Outcome:

No large studies have been performed looking at the association of proton MRS with neurodevelopmental outcome in preterm neonates, probably because of the difficulty of unstable neonates and the technical limitations in acquiring reliable metabolic MRS data throughout the neonatal brain. In preliminary studies, a MR-compatible incubator [27] and a lactate-edited MRSI sequence [28] were used to detect

abnormal metabolite levels following brain injury. This specialized MRSI technique provides two sets of spectral arrays with the resonances of choline, creatine, NAA and lipids in one, and only lactate in the difference spectra. This permits the unambiguous detection of lactate which can be elevated in cases of perinatal hypoxic/ischemic brain injury (Figure 2).

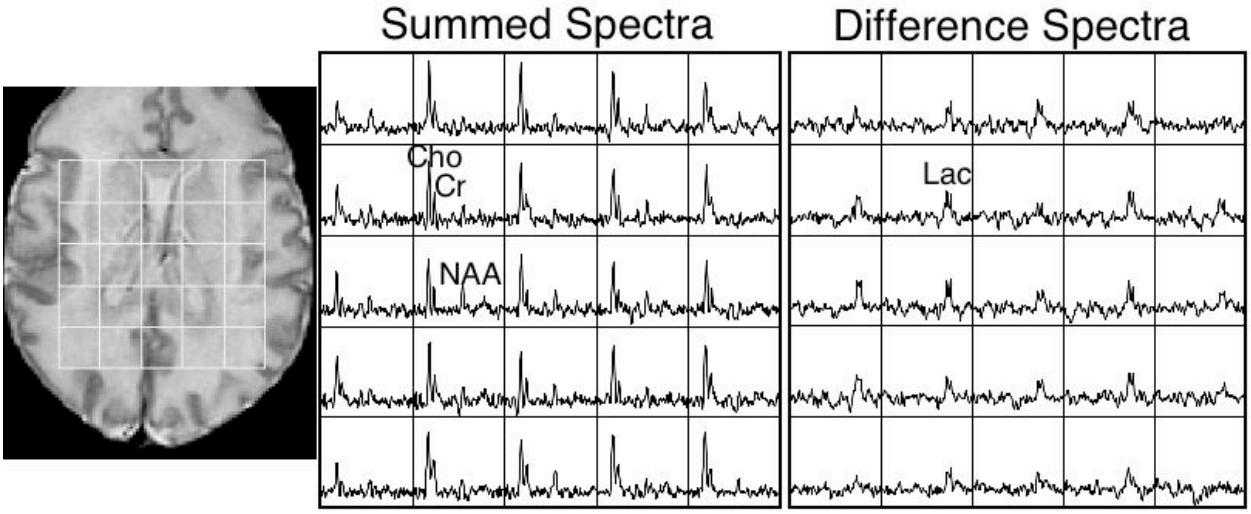

Figure 2. Lactate-edited 3D MRSI data are shown for a neonate with neonatal asphyxia. The summed spectral array shown in the middle include the choline, creatine, NAA and lipid resonances and the difference spectra shown on the right demonstrate just the lactate peaks. Clinical follow-up demonstrated severely abnormal neurologic outcome in this patient.

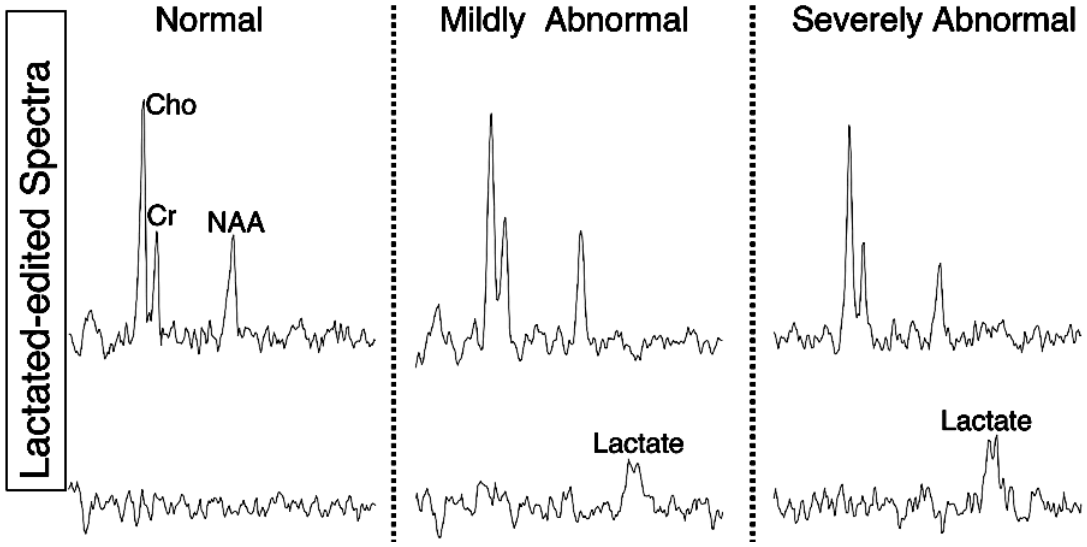

Figure 3. Lactate-edited 3D MRSI data from the basal ganglia are shown for representative patients from each of the three outcome groups. Note the increased lactate in the abnormal outcome groups and reduced NAA in the severely abnormal group.

Our preliminary MRSI studies indicate that NAA values are lower and lactate values higher in preterm neonates with other evidence of brain injury than in preterm neonates who have otherwise normal imaging and development.

Conclusions

The use of metabolic MRS techniques in the evaluation of newborns and infants is still in its early stages, but seems to have great promise. Applications will likely include assessment of brain injury in preterm infants, assessment of brain injury or malformation in encephalopathic term infants, assessment of developmentally delayed infants, and assessment of infants with vasculopathy. A major current challenge is the establishment of ranges of normal values for the different regions of the brain at different ages, so that we can identify those children with mild-to-moderate abnormalities in addition to severely affected children.

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